

Applicants: David Baltimore et al.
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under examination.

In the December 31, 2003 Office Action, the Examiner stated that the application fails to comply with the requirements of 37 C.F.R. §§1.821-825 for the following reasons: the legends of Figures 1, 2A-D, 5A-B and 6A-B referring to nucleotide sequences and/or amino acid sequences of CRAF1 are not accompanied with sequence identification numbers. The Examiner further stated that, in the specification, the amino acid sequence of residues 324-567 of CRAF1 on page 11 is not accompanied by a sequence identification number.

In response, applicants attach hereto a corrected paper copy Sequence Listing as **Exhibit A**, a Computer Readable Form Sequence Listing, and a Statement in Accordance with 37 C.F.R. §1.821(f) as **Exhibit E**. Applicants maintain that the corrected Sequence Listing raises no issue of new matter. In addition, applicants have hereinabove amended the Brief Description of the Figures, and the specification, to refer to sequence identifiers where necessary.

Rejections Under 35 U.S.C. §112 (first paragraph)

The Examiner stated that claims 93-94 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner stated that Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111,

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clearly states that "applicant must convey with reasonably clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the "written description" inquiry, whatever is now claimed." (See page 1117). The Examiner stated that the specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). The Examiner also stated that applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 115). The Examiner further stated that claim 93 is drawn to an isolated protein consisting of consecutive amino acids, the sequence of which amino acid is set forth in SEQ ID NO:2, which protein has the amino acid proline corresponding to the proline at position 568 of SEQ ID NO:2, which protein has the amino acid proline corresponding to the proline at position 568 of SEQ ID NO:2 at its carboxy terminus and extends to the amino acid glycine corresponding to the glycine at position 416 of SEQ ID NO:2. The Examiner also stated that claim 94 is drawn to an isolated protein comprising consecutive amino acids, the sequence of which amino acid is included with SEQ ID NO:1, which protein has the amino acid proline corresponding to the proline at position 567 of SEQ ID NO:1 at its carboxy terminus and extends to at least the amino acid glycine corresponding to the glycine at position 415 of SEQ ID NO:1.

The Examiner stated that claim 93 encompasses a protein consisting of two or three consecutive amino acids set forth in SEQ ID NO: 2, wherein said protein comprises proline corresponding to proline at position 568 of SEQ ID NO:2, and wherein said protein has any

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structure and any length provided it has some consecutive amino acids of SEQ ID NO:2, and has proline and glycine. The Examiner stated that claim 94 encompasses a protein comprising a fragment of SEQ ID NO:1, comprising proline corresponding to proline at position 567 of SEQ ID NO:1 and extends at least to glycine corresponding to glycine at position 415 of SEQ ID NO:1, wherein said protein has any structure and any length provided it comprises a fragment of any length of SEQ NO:1, and has a proline and glycine.

The Examiner stated that although drawn specifically to the DNA art, the findings of *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412) are clearly relevant to the instant rejection. The Examiner stated that the court held that a generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. The Examiner stated that the court indicated that while applicants are not required to disclose every species encompassed by a genus, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. The Examiner stated that at section B(1), the court states that an adequate written description of a DNA... 'requires a precise definition, such as by structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

The Examiner stated that the instant specification however fails to provide sufficient descriptive information, such as definitive

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structural or functional features of the claimed genus of proteins. The Examiner stated that there is no description of the conserved regions which are critical to the structure and function of the genus claimed. The Examiner stated that there is no description of the conserved regions which are critical to the structure and function of the genus claimed. The Examiner stated that there is no description, however, of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The Examiner stated that the structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure. The Examiner stated that, furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed and no identifying characteristic or property of the instant polypeptides is provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. The Examiner stated that in addition, no common functional attributes that identify the claimed genus of proteins are disclosed, because the function of a protein could be abolished, even with substitution of only one amino acid of the protein (Burgess et al. Journal of Cell Biology, 1990, 11:2129-2138).

The Examiner stated that the general knowledge and level of skill in the art do not supplement the omitted description, because specific, not general, guidance is what is needed. The Examiner stated that since the disclosure fails to describe the common attributes or characteristics that identify members of the claimed

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genus of proteins, SEQ ID NO:1 or 2 alone is insufficient to describe the claimed genus of proteins, SEQ ID NO:1 or 2 alone is insufficient to describe the claimed genus of proteins, SEQ ID NO:1 or 2 alone is insufficient to describe the claimed genus of proteins. The Examiner stated that one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of the claimed genus of proteins. The Examiner stated that thus, applicant was not in possession of the claimed genus of proteins.

The Examiner stated that thus, there is insufficient support of claims 93-94 as provided by the Interim Written Description Guidelines published in the June 5, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645. The Examiner stated that therefore, only an isolated polypeptide comprising SEQ ID NO: 1 or 2, but not the full breadth of the claims meets the written description provision of 35 U.S.C. §112, first paragraph.

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include it then
In response, applicants traverse the Examiner's rejection. Specifically, with respect to claim 93, applicants note that the claimed protein consists of consecutive amino acids, the sequence of which amino acids is set forth in SEQ ID NO:2. Thus, contrary to the Examiner's statement that such a protein can consist of two amino acids, i.e. a proline adjacent to a glycine, applicants note that such a sequence is not set forth in SEQ ID-NO:2. Moreover, the claimed protein cannot have "any length" as alleged by the Examiner because the protein consists of consecutive amino acids extending between two defined residues, the sequence of which is set forth in SEQ ID NO:2, as cited in claim 93. Furthermore, the claimed protein cannot have "any structure", as alleged by the Examiner, because

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claim 93 characterizes the claimed protein as consisting of consecutive amino acids, the sequence of which is set forth in SEQ ID NO:2. In addition, claim 93 states that the protein consisting of consecutive amino acids, the sequence of which is set forth in SEQ ID NO:2, extends from a proline corresponding to the proline at position 568 of SEQ ID NO:2 to a glycine corresponding to the glycine at position 416 of SEQ ID NO:2, (this calculates to be a protein consisting of 153 amino acids).

In addition, without conceding the correctness of the Examiner's position, applicants have amended claim 94. Applicants note that the claimed protein consists of consecutive amino acids, the sequence of which amino acids is included in the sequence set forth in SEQ ID NO:1. Applicants further note that the claimed protein cannot have "any structure or any length provided it comprises a fragment of any length of SEQ ID NO:1", as stated by the Examiner, because the sequence of the claimed protein consists of consecutive amino acids, the sequence of which must be included in the sequence set forth in SEQ ID NO:1. This necessarily characterizes both sequence and the length of the claimed protein.

Thus, applicants maintain that claims 93 and 94 comply with the provisions of 35 U.S.C. §112 (first paragraph), and therefore respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §112 (second paragraph)

The Examiner stated that claims 93-94 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to

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particularly point out and distinctly claim the subject matter which applicant regards as the invention. The Examiner stated claims 93-94 are indefinite because it is not clear in claims 93-94 what the size of the consecutive amino acids is.

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In response, applicants traverse the Examiner's rejection. More particularly, applicants have hereinabove pointed out how the structure and length of the consecutive amino acids characterized in claims 93 and 94 is clearly defined by the claims. As asserted by applicants hereinabove, with regard to claim 93, the claimed protein cannot have "any length" as alleged by the Examiner because the protein consists of consecutive amino acids extending between two defined residues, the sequence of which is set forth in SEQ ID NO:2, as cited in claim 93. Furthermore, the claimed protein cannot have "any structure", as alleged by the Examiner, because claim 93 characterizes the claimed protein as consisting of consecutive amino acids, the sequence of which is set forth in SEQ ID NO:2. Moreover, claim 93 states that the protein consisting of consecutive amino acids, the sequence of which is set forth in SEQ ID NO:2, extends from a proline corresponding to the proline at position 568 of SEQ ID NO:2 to a glycine corresponding to the glycine at position 416 of SEQ ID NO:2, thus defining the size of the consecutive amino acids.

With regard to claim 94, applicants note that the claimed protein consists of consecutive amino acids, the sequence of which amino acids is included in the sequence set forth in SEQ ID NO:1. Applicants further note that the claimed protein consists of consecutive amino acids, the sequence of which must be included in the sequence set forth in SEQ ID NO:1. This necessarily

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characterizes both sequence and the length of the claimed protein. Thus, applicants maintain that claims 93 and 94 comply with the provisions of 35 U.S.C. §112 (second paragraph), and therefore respectfully request that the Examiner reconsider and withdraw this ground of rejection.

Rejection Under 35 U.S.C. §102(b)

The Examiner stated that new claims 93 and 94 are rejected under 35 U.S.C. §102(b) pertaining to anticipation by Sato et al. for reasons already of record in paper No.26.

The Examiner stated that claim 93 is drawn to an isolated protein consisting of consecutive amino acids, the sequence of which amino acid is set forth in SEQ ID NO:2, which protein has the amino acid proline corresponding to the proline at position 568 of SEQ ID NO:2 at its carboxy terminus and extends to the amino acid glycine corresponding to the glycine at position 416 of SEQ ID NO:2. The Examiner stated that claim 94 is drawn to an isolated protein comprising consecutive amino acids, the sequence of which amino acid is included within SEQ ID NO:1, which protein has the amino acid proline corresponding to the proline at position 567 of SEQ ID NO: 1 at its carboxy terminus and extends to at least the amino acid glycine corresponding to the glycine at position 415 of SEQ ID NO:1. The Examiner stated that applicant argues that the claimed human peptide in claim 93 is shorter than the human peptide taught by Sato et al.

The Examiner stated that applicant further argues that that SEQ ID NO: 1 is a peptide derived from a mouse, whereas Sato et al.

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discloses two human derived peptides, one of 543 amino acids (full length CRAF-1) and the other of 181 amino acid (a fragment of CRAF1). The Examiner stated that applicant asserts that the specific peptides described in claim 94 contain residue differences with both the fragment and the full length human sequences disclosed by Sato et al. The Examiner stated that applicant asserts that there is a threonine residue at position 390 in the claimed peptide, whereas both the Sato peptides have a methionine at their corresponding position (residue 366 by Sato numbering). The Examiner stated that applicant asserts that there is a further difference at residue 373, with the claimed peptide having an alanine at that position and both the Sato fragments having a valine (residue 349 by Sato's numbering). The Examiner stated that applicant concludes that thus Sato et al. do not anticipate the claimed invention. The Examiner stated that applicant's arguments set forth in paper No. 27 have been considered but are not deemed to be persuasive for the following reasons: claim 93 encompasses a protein consisting of two or three consecutive amino acids as set forth in SEQ ID NO:2, wherein said protein comprises proline corresponding to proline at position 568 of SEQ ID NO:2 and extends to glycine corresponding to glycine at position 416 of SEQ ID NO:2, and wherein said protein has any structure and any length provided it has some consecutive amino acids of SEQ ID NO:2, and has proline and glycine. The Examiner further stated that claim 94 encompasses a protein comprising a fragment of SEQ ID NO: 1, comprising proline corresponding to proline at position 567 of SEQ ID NO:1 and extends at least to glycine corresponding to glycine at position 415 of SEQ ID NO:1, wherein said protein has any structure and any length provided it comprises a fragment of any length of SEQ ID NO:1, and has proline and glycine. In addition, the Examiner stated that the

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sequence taught by Sato et al. has some consecutive amino acids of SEQ ID NO: 1 and 2, and has proline and glycine, and thus seems to be the same as the claimed sequences, and meets all the limitation of the claims.

The Examiner stated that concerning claim 93, the length of the sequence is not recited in the claim, and thus applicants argue a limitation not in the claim.

The Examiner stated that concerning claim 94, the claimed protein does not recite threonine at position 390, and alanine at position 373, which are outside of the positions 415 to 567 of SEQ ID NO:1. The Examiner stated that thus applicants argue a limitation not in the claim.

In response, applicants traverse the Examiner's rejection. Specifically, with regard to claim 93, applicants note that the shorter of the two fragments disclosed by Sato et al. is the 181 C-terminal residues of CRAF-1, residues 363-543 by Sato's numbering (i.e. equivalent in number of residues to positions 388-568 of SEQ ID NO:2). Applicants note that the amino acid sequence of the 181 residue polypeptide disclosed by Sato et al. does not consist of a sequence set forth SEQ ID NO:2, which sequence extends from a proline corresponding to the proline at position 568 of SEQ ID NO:2 to a glycine corresponding to the glycine at position 416 of SEQ ID NO:2. In fact, the 181 residue polypeptide disclosed by Sato et al. extends from a proline at equivalent position 568 of SEQ ID NO:2 to well beyond the glycine corresponding to the glycine at position 416 of SEQ ID NO:2.

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In addition, without conceding the correctness of the Examiner's position, applicants have amended claim 94. Applicants note that claim 94 as amended states the claimed protein consists of consecutive amino acids, the sequence of which amino acids is included in the sequence set forth in SEQ ID NO:1. Applicants note that none of the polypeptides disclosed by Sato et al. consist of consecutive amino acids having a sequence included in the sequence set forth in SEQ ID NO:1. In light of this, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

In summary, in light of the remarks made hereinabove, applicants respectfully request that the Examiner reconsider and withdraw the various grounds of rejection set forth in the December 31, 2002 Final Office Action.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.


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No fee is deemed necessary in connection with the filing of this Amendment. If any such fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,



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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Honorable Commissioner for Patents and Trademarks, Washington, D.C. 20231, BOX AF	
	3/31/03
John P. White Reg. No. 28,678	Date



50659

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Asp Gln Thr Leu Ser Val His Asp Ile Arg Leu Ala Asp Met Asp Leu
35 40 45

Arg Phe Gln Val Leu Glu Thr Ala Ser Tyr Asn Gly Val Leu Ile Trp
50 55 60

Lys Ile Arg Asp Tyr Lys Arg Arg Lys Gln Glu Ala Val Met Gly Lys
65 70 75 80

Thr Leu Ser Leu Tyr Ser Gln Pro Phe Tyr Thr Gly Tyr Phe Gly Tyr
85 90 95

Lys Met Cys Ala Arg Val Tyr Leu Asn Gly Asp Gly Met Gly Lys Gly
100 105 110

Thr His Leu Ser Leu Phe Phe Val Ile Met Arg Gly Glu Tyr Asp Ala
115 120 125

Leu Leu Pro Trp Pro Phe Lys Gln Lys Val Thr Leu Met Leu Met Asp
130 135 140

Gln Gly Ser Ser Arg Arg His Leu Gly Asp Ala Phe Lys Pro Asp Pro
145 150 155 160

Asn Ser Ser Ser Phe Lys Lys Pro Thr Gly Glu Met Asn Ile Ala Ser
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Gly Cys Pro Val Phe Val Ala Gln Thr Val Leu Glu Asn Gly Thr Tyr
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Arg Gln Lys Glu Met Leu Arg Asn Asn Glu Ser Lys Ile Leu His Leu
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Glu Ile Arg Pro Phe Arg Gln Asn
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Phe Glu Glu Leu Pro Cys Leu Arg Ala Asp Cys Lys Glu Lys Val Leu
35 40 45

Arg Lys Asp Leu Arg Asp His Val Glu Lys Ala Cys Lys Tyr Arg Glu
50 55 60

Ala Thr Cys Ser His Cys Lys Ser Gln Val Pro Met Ile Lys Leu Gln
65 70 75 80

Lys His Glu Asp Thr Asp Cys Pro Cys Val Val Val Ser Cys Pro His
85 90 95

Lys Cys Ser Val Gln Thr Leu Leu Arg Ser Glu Leu Ser Ala His Leu
100 105 110

Ser Glu Cys Val Asn Ala Pro Ser Thr Cys Ser Phe Lys Arg Tyr Gly
115 120 125

Cys Val Phe Gln Gly Thr Asn Gln Gln Ile Lys Ala His Glu Ala Ser
130 135 140

Ser Ala Val Gln His Val Asn Leu Leu Lys Glu
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Ala Ala Leu Leu Ser Ser Ser Ser Pro Lys Cys Thr Ala Cys Gln Glu
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Ser Ile Ile Lys Asp Lys Val Phe Lys Asp Asn Cys Cys Lys
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20 25 30

Leu Gln Asn Arg Val Thr Glu Leu Glu Ser Val Asp Lys Ser Ala Gly
35 40 45

Gln Ala Ala Arg Asn Thr Gly Leu Leu Glu Ser Gln Leu Ser Arg His
50 55 60

Asp Gln Thr Leu Ser Val His Asp Ile Arg Leu Ala Asp Met Asp Leu
65 70 75 80

Arg Phe Gln Val Leu Glu Thr Ala Ser Tyr Asn Gly Val Leu Ile Trp
85 90 95

Lys Ile Arg Asp Tyr Lys Arg Arg Lys Gln Glu Ala Val Met Gly Lys
100 105 110

Thr Leu Ser Leu Tyr Ser Gln Pro Phe Tyr Thr Gly Tyr Phe Gly Tyr
115 120 125

Lys Met Cys Ala Arg Val Tyr Leu Asn Gly Asp Gly Met Gly Lys Gly
130 135 140

Thr His Leu Ser Leu Phe Phe Val Ile Met Arg Gly Glu Tyr Asp Ala

145 150 155 160
 Leu Leu Pro Trp Pro Phe Lys Gln Lys Val Thr Leu Met Leu Met Asp
 165 170 175
 Gln Gly Ser Ser Arg Arg His Leu Gly Asp Ala Phe Lys Pro Asp Pro
 180 185 190
 Asn Ser Ser Ser Phe Lys Lys Pro Thr Gly Glu Met Asn Ile Ala Ser
 195 200 205
 Gly Cys Pro Val Phe Val Ala Gln Thr Val Leu Glu Asn Gly Thr Tyr
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Leu Pro Asp Pro

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 <211> 153
 <212> PRT
 <213> MOUSE SP.

<400> 11

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 20 25 30

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 35 40 45

Gly Met Gly Lys Gly Thr His Leu Ser Leu Phe Phe Val Ile Met Arg
 50 55 60

Gly Glu Tyr Asp Ala Leu Leu Pro Trp Pro Phe Lys Gln Lys Val Thr
 65 70 75 80

Leu Met Leu Met Asp Gln Gly Ser Ser Arg Arg His Leu Gly Asp Ala
 85 90 95

Phe Lys Pro Asp Pro Asn Ser Ser Ser Phe Lys Lys Pro Thr Gly Glu
 100 105 110

Met Asn Ile Ala Ser Gly Cys Pro Val Phe Val Ala Gln Thr Val Leu
 115 120 125

J1
4
Glu Asn Gly Thr Tyr Ile Lys Asp Asp Thr Ile Phe Ile Lys Val Ile
130 135 140

Val Asp Thr Ser Asp Leu Pro Asp Pro
145 150



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Mark-up Copy of the Amendments To The Brief Description of the
Figures

The Brief Description of the Figures has been amended as follows:

Figure 1. Predicted amino acid sequences of mouse (M) (SEQ ID NO:1) and human (H) (SEQ ID NO:2) CRAF1. The full-length mouse sequence is shown and numbered. The human sequence has one more amino acid than that of the mouse (indicated with a dot), but all numbers here refer to the mouse sequence. Dashes indicate positions in the human sequence that are identical to those in the mouse. The C26 clone obtained from the yeast two-hybrid screen contained the COOH-terminal region of CRAF1 starting from the position marked with an arrow.

Figures 2A-D. Potential structural domains of CRAF1. (A) Diagrams of three TRAF family members. Percentages of amino acid identity between CRAF1 and either TRAF1 or TRAF2 are shown. The TRAF domain was defined in the COOH-terminal region of TRAF1 and TRAF2(19) (residues 356 to 562 for CRAF1 (SEQ ID NO:6)) but can be subdivided into TRAF-N and TRAF-C subregions according to sequence homology with CRAF1 as well as by the mapping assaying shown in Fig. 3. For CRAF1 (SEQ ID NO:1), the number of amino acids between homologous regions is indicated. (B) Helical wheel representation of residues 287 to 342 of CRAF1 (SEQ ID NO:7). The wheel starts with the inner residue Ile²⁸⁷ at position a and diminishes with the outer residue Asn³⁴² at position g; "+" and "-" denote change of amino acid residues. (C) Predicted Zn fingers corresponding to residues 110

to 264 of CRAF1 (SEQ ID NO:8). (D) Zn finger from residues 45 to 106 of CRAF1 (SEQ ID NO:9). n, NH₂-terminus; c, COOH-terminus.

Figures 5A-B. cDNA nucleotide sequence and predicted amino acid sequences of mouse CRAF1 (SEQ ID NO:4). The cDNA nucleotide sequence is also deposited in GenBank with accession number U21050.

Figures 6A-B. cDNA nucleotide sequence and predicted amino acid sequences of human CRAF1 (SEQ ID NO:5). The cDNA nucleotide sequence is also deposited in GenBank with accession number U21092.



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The paragraph starting on page 11, line 10, as follows has been amended as follows:

--Variants within the scope of the invention include proteins and peptides with amino acid sequences having at least eighty percent homology with the COOH-terminal domain of CRAF1 (corresponding roughly to residues 415-567 (SEQ ID NO:12)) or with C26 (residues 324-567 of CRAF1 (SEQ ID NO:11)). More preferably the sequence homology is at least ninety percent, or at least ninety-five percent.--



Mark-up Copy of the Claims

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The paragraph starting on page 11, line 10, as follows has been amended as follows:

--94. (Amended) An isolated protein consisting of [comprising] consecutive amino acids, the sequence of which amino acids is included within the sequence set forth in SEQ ID NO:1, which protein has the amino acid proline corresponding to the proline at position 567 of SEQ ID NO:1 at its carboxy terminus and extends to [at least] the amino acid glycine corresponding to the glycine at position 415 of SEQ ID NO:1.---



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Applicants : David Baltimore et al.
Serial No. : 08/813,323 (CPA) Examiner: Minh-Tam Davis
Filed : March 10, 1997 Group Art Unit: 1642
For : TRUNCATED CRAF1 INHIBITS CD40 SIGNALING

1185 Avenue of the Americas
New York, New York 10036
March 24, 2003

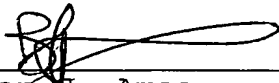
Sir:

STATEMENT IN ACCORDANCE WITH 37 C.F.R. §1.821(f)

In accordance with 37 C.F.R. §1.821(f), I hereby certify that the computer readable form containing the nucleic acid and/or amino acid sequences required by 37 C.F.R. §1.821(e) and submitted herewith contains the same information as the written "Sequence Listing" (13 pages) (Exhibit A) that is submitted herewith.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such wilful false statements may jeopardize the validity of the application or any patent issued thereon.

Respectfully submitted,



Brian U. Amos
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